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Herpesvirus claims another elephant as search for answers continues

With few resources, researchers work to contain fatal elephant virus



Elephant endotheliotropic herpesviruses were first identified in 1995 when Kumari (above) died suddenly of EEHV infection at the National Zoological Park.

Courtesy of Jessie Cohen/Smithsonian National Zoological Park

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By R. Scott Nolen

This past May the Berlin Zoo announced that Ko Raya, a 2-year-old female Asian elephant, had died of an infection caused by a particularly virulent species of herpesvirus discovered only within the past two decades.

With few exceptions, herpesviruses don't cause clinically important disease. The virus that caused Ko Raya's death, however, was one of several novel elephant endotheliotropic herpesviruses now considered among the most serious challenges to the Asian elephant's survival in captivity and the wild. No vaccine is available for EEHV, nor are there any reliable treatment options for the disease, which accounts for a quarter of young, captive Asian elephant deaths.

Many of the 12 species of herpesviruses carried by elephants are benign. What sets the EEHVs

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apart is their lethality. Elephant endotheliotropic herpesviruses can cause a hemorrhagic illness so severe as to result in death within 24 hours of onset. The odds of surviving systemic EEHV viremia are approximately 20 percent, and just eight elephants have done so.

Dr. Ellen Wiedner was director of veterinary care for the Ringling Bros. and Barnum & Bailey Center for Elephant Conservation in 2010 when an Asian calf at the Florida facility suddenly "wasn't acting right." When a young elephant is lethargic or otherwise not behaving normally, one of the first concerns is EEHV infection, according to Dr. Wiedner, who recently joined the Los Angeles Zoo.

"There are plenty of ugly diseases that kill baby elephants, but this one is terrifying. This is the one we all worry about," she said.

The calf eventually recovered after an aggressive treatment regimen that included famciclovir and intensive supportive care. In this and the seven other cases of EEHV survival, no one can say with certainty whether the antiviral therapy, intensive care management, or the animal's immune system was most responsible for their survival. It's one of several questions that have gone unanswered since 1995, when Kumari, a 16-month-old Asian calf at the Smithsonian's National Zoological Park in Washington, D.C., became the first known EEHV fatality.

Since Kumari's death, a network of veterinarians, virologists, and conservationists have shed light on EEHVs, of which seven species have been identified. Together they form a newly designated genus of mammalian herpesviruses known as probosciviruses. Five species are associated with disease and death, but only one—EEHV1—accounts for 90 percent of all the deaths and serious illnesses.

EEHV research received a major boost when the National Elephant Herpesvirus Laboratory was established in 2004 at the National Zoo. Today, the facility is a major resource for EEHV research and testing around the world.

Herpesviruses are unlike some other viruses, explained laboratory manager Erin Latimer, in that they don't normally kill their hosts.

"They have co-evolved with their hosts over millions of years and have a symbiotic relationship," she said. Latimer considers these novel herpesviruses a serious threat not only to captive Asian elephants but also to herds in the wild, where the disease's impact is just beginning to be understood.

Because so much about the viruses is still a mystery, veterinarians dealing with an elephant in the early stages of EEHV disease have neither the means for quickly diagnosing the infection nor any proven treatment options to prescribe. "We're really at the very beginning stages of understanding this virus," Dr. Wiedner said. "We don't understand its epidemiology, and we need to know more about the pathogenesis." She suspects severely infected elephants are dying of shock and organ failure.

Fatal EEHV disease has been traced back to the early 1980s. At least 50 Asian elephant deaths in North America and Europe were a result of EEHV viremia. In addition, the herpesviruses are linked to 24 wild and captive elephant fatalities in India, Thailand, and Cambodia, although the actual number of elephants dying of the viral disease in these regions is thought to be much higher.

Three species of EEHVs have also been identified in lung and skin nodules from healthy African elephants. These findings suggest African elephants could be a natural host for some

"There are plenty of ugly diseases that kill baby elephants, but this one is terrifying. This is the one we all worry about." —Dr. Ellen Wiedner, who treated one of only eight elephants to survive severe elephant endotheliotropic herpesvirus infection



Sri Lankan scientists are collaborating with the National Elephant Herpesvirus Laboratory to shed light on the impact EEHVs are having on Asian elephants in the wild.

Courtesy of Arranda Perez/Smithsonian National Zoological Park

elephant from extinction, according to Deborah Olson, executive director of the International Elephant Foundation. Olson estimates 270 Asian elephants are currently being managed in North America, with about the same number in Europe. In countries where the elephants are indigenous, their numbers are dwindling as a consequence of natural and man-made pressures, such as poaching, loss of habitat, and predation. According to Kristine Schad, a population biologist with the Association of Zoos and Aquariums, AZA-accredited institutions in North America saw a mean of 3.2 Asian elephant calf births per year between 2000 and 2010.

These low numbers, Olson says, can't compensate for the natural death rate of this aged population of managed elephants. "What we will see in the future is a steep decline of the population and then a very, very slow increase in numbers as the younger population reproduces. Obviously this is where EEHV has a very negative impact, because if we lose many of this younger generation, we will have little to work with to rebuild the population," explained Olson, whose IEF supports EEHV research partly with donations from U.S. elephant-holding facilities.

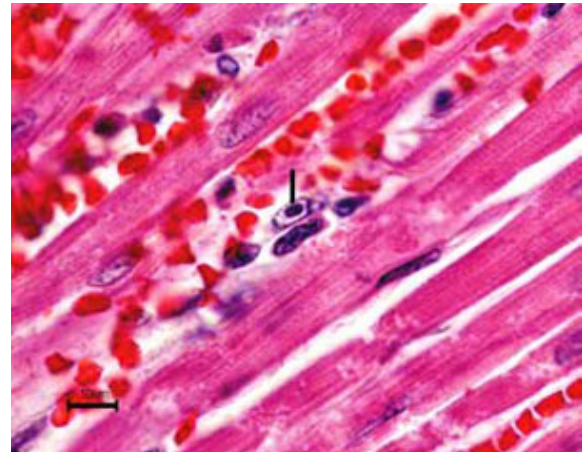
Low numbers of Asian elephant births, combined with a high calf mortality rate, makes Dr. Jeff Stanton wonder whether most of the captive Asian elephant population will be wiped out within 40 years. Dr. Stanton has been studying elephant herpesviruses for the past two years at

of these herpesviruses, which may explain their lethality in Asian elephants.

Young Asian elephants are particularly vulnerable to the viruses, with most infections occurring in elephants 1 to 4 years old. Gary Hayward, PhD, a research scientist at Johns Hopkins University, is considered a pioneer in the study of elephant endotheliotropic herpesviruses. He says up to a quarter of all captive Asian elephants 2 months of age and older die of EEHV disease. Over the past two years alone, six calves managed at institutions in England and Germany have died of herpesvirus infections, including Ko Raya.

"EEHV1 disease could not be called epidemic in the true biological sense of spreading rapidly from one individual to others in successive waves," Dr. Hayward said. "There is no linear chain of transmission here, but, in effect, the fact that the disease is killing 20 to 25 percent of all Asian elephant calves that live at least two months, then yes, it does seem to be of epidemic proportions."

EEHVs are one of several factors undermining efforts to save the Asian



Viral inclusion bodies in endothelial cells are a hallmark of herpesvirus infection.

Courtesy of Smithsonian National Zoological Park

Baylor College of Medicine, near the Houston Zoo. In 2008 Mac, a 2-year-old Asian elephant, died of EEHV infection at the zoo. The two institutions partnered with the goal of developing a test for the disease and possibly even a vaccine.

A team of more than 20 people are part of Baylor's EEHV project, which has led to the creation of a quantitative real-time PCR assay capable of detecting the virus in blood. The test has aided the discovery of EEHV1 DNA in trunk washes from four captive herds of healthy Asian elephants, suggesting at least some species of the herpesviruses are endemic in these populations. "My opinion is that the vast majority of Asian elephants are infected with at least one, and probably more than one, of the seven known EEHVs," Dr. Stanton said.

Baylor is also near to sequencing the EEHV1 genome. The process has been a challenge, explained Paul Ling, PhD, an associate professor in Baylor's Department of Molecular Virology and Microbiology, who is overseeing the work, since the genetic makeup of the Asian elephant is unknown. Moreover, the genetic sequences of EEHVs are unidentified and are highly divergent from the sequences of most other herpesviruses, meaning no comparable templates are available to build on.

"It's a bit like looking for a needle in a stack of needles in a haystack," Dr. Ling said. Mapping the virus's DNA could yield a better understanding of how the herpesviruses establish lifelong infections. Important proteins may also be identified, aiding in the development of a vaccine.

The chances of an EEHV vaccine being developed within the next 10 years are remote, however. Next to nothing is known about elephant immunology, and growing EEHVs in cell culture has proved especially difficult. Aside from the research challenges, the funding necessary to sustain such a long-term endeavor isn't there. The IEF's Deborah Olson says the government has so far shown little interest in supporting elephant herpesvirus research, and the small number of captive elephants means there's no profit for pharmaceutical companies in developing an EEHV vaccine.

"This lack of attention makes attracting funding to EEHV instead of these other hot-button issues that much more difficult," Olson said. Learn more about EEHV and related research initiatives at www.elephantconservation.org.

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